SECURITY OF THE SUPPLY CHAIN: AN AUDITOR'S PERSPECTIVE

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INTRODUCTIONS:

Twenty-eight years of Pharmaceutical Regulatory experience, including senior management positions for several biopharmaceutical companies including Pasteur-Merieux (now Sanofi-Aventis), PA Biologicals, Estendart, ChiwiBio, Hornetcorn, etc.

Highly respected Quality Assurance, Quality Control expert in China since 2009, with successfully bringing three products to WHO Pre-qualification.

Knowledge of US FDA, CFDA and EMEA regulations.

ETRS Certified Auditor performing cGMP/GLP/ISO investigations, due diligence and training.

Biologics – 90% Biotech, Biosimilars, Fractionation, Immunotherapy, Monoclonal Antibodies, Vaccines

Pharmaceuticals – 10 % Antibiotics, API, Excipients, Orphan Drugs, Sterile Dosage Forms, Tablets
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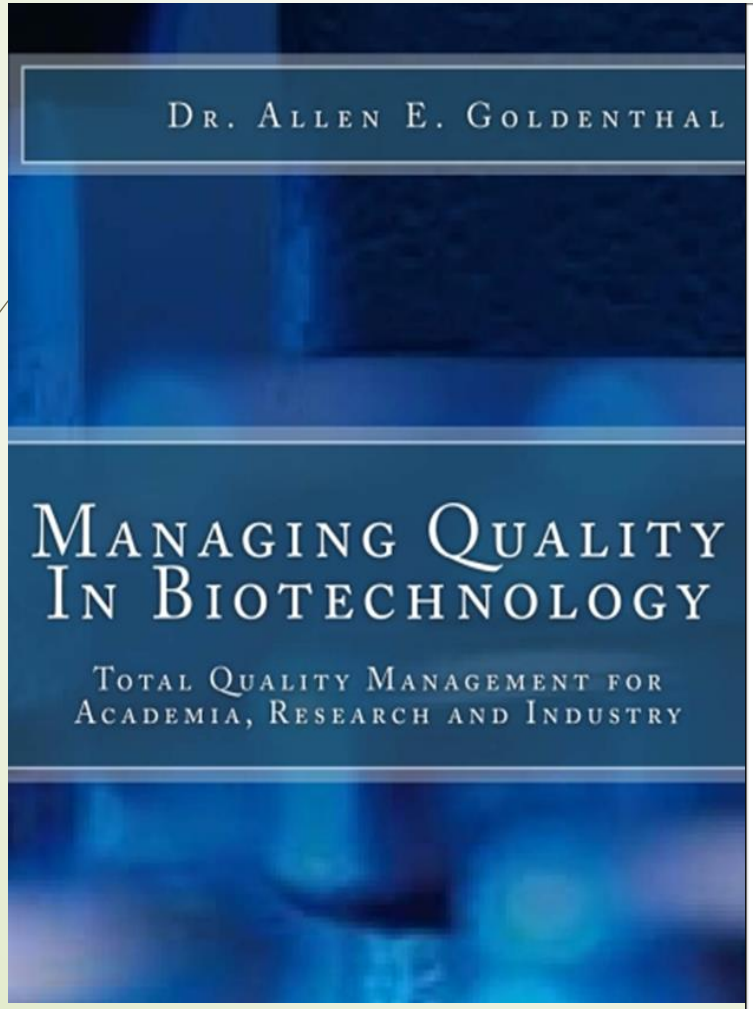

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Managing Quality in Biotechnology is unique in its approach to Total Quality Management (TQM) as it adopts an insider's view of what is crucial and important in the day-to-day operations of bio-related laboratories at both an academic research level as well as by a full production facility. Most reference books on TQM have been written specifically for the commercial production facility and have not addressed that quality must begin at inception of the initial concept and that relies on it being implemented all the way back to the primary investigator in his university or company laboratory. Though the research laboratory operates at a much smaller scale and modality, still all the essential requirements and expectations of TQM and Good Manufacturing Practices (GMP) apply. Ensuring that initial research and development meets the expectations of safety, efficacy and potency is why TQM is probably even more important within academic institutions. The absence of guidelines being applied to the university and developmental laboratory environments makes this book an essential part of any research library. It is a comprehensive reference book for university students, a hands-on manual for laboratory technicians, and a practical guide for biopharmaceutical managers.

GENERAL OVERVIEW:

- Principles of Supply Chain Management System Auditing
- Requirements for Auditing
- Managing an External Audit Program
- Dealing with the Auditees
- Planning an External Audit
- Conducting an External Audit
- Managing the Audit Findings
- Post-Audit Activities
- The Need and Requirement of a Quality Agreement

THE QUALITY MANAGEMENT SYSTEM:

- Include procedures to verify that any supplier of excipients has the capability to consistently meet requirements
- Include the requirement for periodic audits
  a) Self or 3rd Party
  b) Paper audits are no longer acceptable for critical materials
  c) Need to have oversight of supplier sub-contracts used in any part of the process
- Confirm that the agreed upon supply chain is in tact
- Integrity of packaging and seals must be carried out

PRINCIPLES OF MANAGEMENT SYSTEM AUDITING OF SUPPLIERS:

Why Auditing of Suppliers is Essential:

- It provides the opportunity to ensure that the supplier has effectively implemented a Quality Management System
- Identifies areas of conformity and nonconformity with your own requirements, applicable regulatory requirements and benchmarked against your own Quality Systems.
- Provides a systematic discipline for corrective and preventive actions to meet those requirements.

THE GUIDING PRINCIPLE:

Auditing the entire length of the supply chain is essential:

To determine through an unbiased means and through factual information based on quality performance, whether the quality system is effective in maintaining control by checking that prescribed quality objectives are being achieved and the resultant products and services meet your company's specified and regulatory requirements.

KNOW THE TERMS AND DEFINITIONS:

Audit: A systematic, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which audit criteria are fulfilled.

Audit Criteria: Set of policies, procedures or requirements used as a reference against which audit evidence is compared.

Audit Evidence: Records, statements of fact or other information which are relevant to the audit criteria and verifiable.

DEFINITIONS CONTINUED:

Audit Findings: Results of the evaluation of the collected evidence against the audit criteria.

Audit Conclusions: The outcome of the audit provided by an 'Audit Team' after consideration of the audit objectives and audit findings.

Auditor: Persons with competence, that have successfully undergone and passed the appropriate training to conduct an audit.

Audit Scope: The extent and boundaries of an audit, which generally include a description of physical locations, organizational units, activities and processes, as well as the time period covered.

Audit Program: A set of one or more audits planned for a specific timeframe and with a specific purpose.

DEFINITIONS CONTINUED:

Audit Plan: A description of the actual activities to be performed during the audit.

Auditee: The supply organization being audited.

Audit Client: Which part of your organization or 3rd party requested the audit.

Competence: This is a subjective assessment often overlooked by auditors in which they must examine the personal attributes of the people performing tasks and decide if they have demonstrated the ability to apply knowledge and skills suitably.

7 KEY REQUIREMENTS TO SUCCESSFUL AUDITING

REQUIREMENTS FOR AUDITING:

1. **Ethical Conduct:**

   Audits must be conducted in a professional manner to achieve;

   a) Trust
   b) Integrity
   c) Confidentiality
   d) Discretion

   These are Essential for a successful audit and not everyone is suitable for the conduct of an audit.

REQUIREMENTS FOR AUDITING:

2. Fair Play:

It is obligatory to report in a truthful and accurate manner;

a) Audit activities to be agreed upon and not seen to drift in other directions.

b) Obstacles not to be placed in the way of the audit.

c)Any unresolved divergent opinions need to be addressed carefully and an agreement needs to be arrived at.

REQUIREMENTS FOR AUDITING:

3. **Professionalism:**

   The need for diligence and application of proper judgment is essential in auditing.

   a) Auditors must have the necessary competence in the area they are auditing.

   b) Knowledge is not necessarily the same as being right. The skill is to examine the situation from alternative angles.

   c) Stick to the facts.

REQUIREMENTS FOR AUDITING:

4. **Independence:**

   Impartiality can only be achieved if the auditor is fully independent of the auditee.

   a) Auditors must be free of bias and any conflict of interest.

   b) Objectivity over subjectivity but an opinion still counts as long as it is identified as an opinion.

   c) Exchange of courtesies is fine, but an exchange of gifts is unacceptable.

REQUIREMENTS FOR AUDITING:

4. **Evidence Based Approach:**

   Only make statements that you can provide verification for.

   a) Findings should have a degree of repeatability. A one-off issue does not necessarily mean it is a significant finding.

   b)Findings are only to be based on evidence uncovered during the audit.

   c) Provide several samples of evidence for every stated observation, otherwise it may only be a comment.

REQUIREMENTS FOR AUDITING:

5. **Proper Preparation of the Audit:**
   Prior to the audit, define all the objectives. Define the extent of the audit based on the size, nature and complexity of the organization being audited. Establish the program.
   a) Number of auditors and the responsibility of each.
   b) Prepare the necessary resources. Checklists, SOPs, logs, etc.
   c) Ensure that each auditor is qualified in their respective areas of expertise.

REQUIREMENTS FOR AUDITING:

6. Personal Preparation by the Auditor:

Ensure that the auditor have read and understood the QMS documentation on auditing.

a)Auditor checks that his audit kit is complete with the audit plan, any previous audit reports, follow up actions to be confirmed, checklist or notepad.

b) Copy of the Standards for the area being audited and Quality Agreement

c) Identification of key activities to be monitored and assessed.

REQUIREMENTS FOR AUDITING:

7. **Know when the audit is over:**

   The audit is not over until all the objectives have been met and any findings requiring corrective actions have been dealt with appropriately.

   a) Time management is essential.

   b) Discussions must be limited and only allowed of pertinent and relevant.

   c) Any disagreements are handled post-audit and not during audit time.

   d) Do not permit the auditee take control of the audit.

   d) The Customer 'IS IMPORTANT'

THE QUALITY AGREEMENT:

The PIC/S Guide to GMP, Clause 5.26, recommends that manufacturers discuss all quality requirements and expectations for starting materials with the supplier.

The Quality Agreement formalizes any discussions and clarifies expectations of both parties.

For example:

Specified materials, services or situations (e.g. in the event of a quality failure in material); Access to the supplier's manufacturing site for audit with respect to GMP and quality expectations; Requirements to ensure traceability; Expectations for storing reference/retention samples;

Access to manufacturing and/or laboratory records; Rules concerning subcontracting; Requirements to minimize crosscontamination or other qualityrelated issues; Rules concerning implementation of corrective actions by the supplier;

QUALITY AGREEMENT CONTINUED:

AND:
Notification of changes to the manufacturing process, site, equipment, testing methods, specifications, supplier/third party, any other quality related parameters that could impact the quality of the starting material. Any change must be approved by the manufacturer before accepting supply.

Changes to a GMP agreement may occur at the time a supplier notifies the manufacturer of a change (e.g. change in process or testing) or at the next scheduled update to the agreement.

RESPONSIBILITIES OF THE QUALITY AGREEMENT:

Responsibilities	Supplier	Customer	NA
Conform to the GMP Guide and/or other quality criteria defined in the scope of this agreement. The current versions of the defined quality criteria in effect at the time of this agreement are attached. (Attachment of quality criteria is optional.)	X	X	
Mutually agree upon specifications for the materials which are the subject of this agreement. Specifications in place at the time of this agreement are attached. (Attachment of specifications is optional.)	X	X	
Changes to the agreed upon specifications must be mutually agreed upon and communicated in writing between the parties to this agreement, except for compendial changes which can be implemented without mutual agreement.	X	X	

RESPONSIBILITIES OF THE QUALITY AGREEMENT:

Responsibilities	Supplier	Customer	NA
Ensure that the specifications for compendial materials are in compliance with the current compendia.	X	X	
Manufacture materials or provide services that conform to the mutually agreed upon specifications.	X		
Upon request, disclose to the Customer recent regulatory agency inspections and findings pertaining to the materials or services.	X		
Notify promptly if, in the course of a regulatory inspection, negative findings are made related to the quality of the materials or services supplied.	X	X	
Shall have a quality agreement with third parties used for production, packaging, testing or processing the materials in any manner, which could be viewed during an audit.	X		

RESPONSIBILITIES OF THE QUALITY AGREEMENT:

Responsibilities	Supplier	Customer	NA
Document that manufacturing and packaging process are fit for purpose. Demonstrate the commissioning of critical systems and equipment used in the manufacture and control of the Excipient. Demonstrate that cleaning procedures are appropriate and their effectiveness has been demonstrated.	X		
Samples will be retained for a period of ____ years from _____ (specify).	X		
Agree upon special labelling requirements.	X	X	

QUALITY AGREEMENT RECORDS:

Documentation and Records	Supplier	Customer	NA
Certificate of Analysis will be supplied with each batch.	X		
Certificate of Analysis will be prepared either according to the current Certificate of Analysis Guide for Pharmaceutical Materials or an agreed upon alternative that is defined in this agreement (an example COA may be attached).	X		
Agree upon special Certificate of Analysis requirements.	X	X	
Where applicable, electronic signatures used on the Certificates of Analysis must conform to the requirements of the Regulatory Agencies.	X		
Records required by the agreed upon quality system will be maintained for a period of ____ years from _____ (specify).	X		

QUALITY AGREEMENT RECORDS:

Documentation and Records	Supplier	Customer	NA
Storage and Distribution			
Maintain and supply upon request documentation that supports the recommended storage and transportation conditions plus reevaluation or expiry dates.	X		
Ensure that Excipients are stored and shipped in accordance with manufacturer's recommended storage conditions.	X	X	
Where applicable, agree upon requirements for reusable shipping containers.	X	X	

QUALITY AGREEMENT CHANGE CONTROL:

Documentation and Records	Supplier	Customer	NA
Change Control			
Changes will be evaluated and communicated based upon agreed criteria and timelines. The Supplier must have an established change control system that is reviewed and approved by the Customer.	X		

QUALITY AGREEMENT NON-CONFORMANCE:

All non-conformance should be investigated. Where applicable this includes the identification of the root cause, a risk analysis (including the risk to other lots and the impact to other test results) of the actions taken for correction of the problem, prevention of future occurrence and the formal conclusion by Supplier's Quality Assurance. If an investigation reveals that there is an impact to materials or services received by the Customer, Supplier shall inform Customer without unreasonable delay.
Out-of-specification (OOS) test results should be investigated and documented according to a documented procedure.
If significant deviations from an established process are recorded, there should be evidence of suitable investigations and a review of the quality of the Excipients.

QUALITY AGREEMENT COMPLAINTS AND RECALLS:

Complaints
Supplier must have a written procedure to investigate and document quality related complaints. A root cause analysis, actions taken for correction of the problem, prevention of future occurrence and the formal conclusion will be provided to the Customer within a reasonable time after receipt of the complaint.
Complaints made shall at least indicate the Supplier's batch number of the material and complaint subject. The complaint shall be communicated to the Supplier within a reasonable time after receipt of the material. Samples will be provided where appropriate and available.
The parties shall cooperate in the exchange of information required to effectively conduct an investigation.
Recalls
In the case of a recall, the Supplier shall inform Customer without unreasonable delay of the planned recall.
The Supplier must have a written recall procedure.
Customer shall notify Supplier of any finished product recall which was investigated or is under investigation and has potential to be related to the quality of the materials or service, as soon as possible.

QUALITY AGREEMENT ON AUDITING:

Responsibilities	Supplier	Customer	NA
Auditing			
Have the right to audit Supplier's facilities, systems and documentation, as they relate to the materials or services provided, at mutually agreed upon times.		X	
Allow Customer to audit facilities, systems and documentation, as they relate to the manufacture of Excipients, at mutually agreed upon times.	X		
If required, a confidentiality agreement will be executed within a reasonable period of time prior to the audit.	X	X	
Customer shall issue a confidential written audit report to the Supplier, which will include audit observations, within X days (mutually agreed upon timeline).		X	

QUALITY AGREEMENT ON AUDITING:

Responsibilities	Supplier	Customer	NA
Auditing			
Supplier shall issue responses within X days (mutually agreed upon timeline) to all observations in writing to Customer Quality Assurance. Where the Supplier commits to a corrective action, a description and timeframe for completion will be included in the written response.	X		
Where applicable, agree upon requirements for auditing third parties used in association with excipients production, processing, warehousing, or testing.	X	X	

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